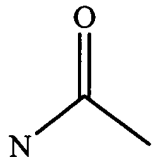
IN THE CLAIMS

1. (Currently amended) A bisubstrate inhibitor of insulin receptor kinase, comprising:

a ~~nucleotide or~~ nucleotide analog moiety ~~comprising a triphosphate~~ consisting of γ-S-ATP; and

a peptide moiety which is a substrate for said insulin receptor kinase and which comprises ~~a tyrosine residue or~~ a 2-amino-3-(4-amino-phenyl)-propionic acid residue;

wherein said moieties are linked by a tether, wherein said tether is linked ~~to the tyrosine residue via its phenolic oxygen or~~ to the 2-amino-3-(4-amino-phenyl)-propionic acid residue via its aniline nitrogen and wherein said tether is linked to the ~~nucleotide or~~ nucleotide analog moiety via the gamma phosphate of said γ-S-ATP ~~the triphosphate~~, wherein the tether is



~~greater than or equal to 4.9 Å measured from a gamma phosphorus of the nucleotide or nucleotide analog moiety to a proton donor of the tether formed by the phenolic oxygen or the aniline nitrogen~~.

2. (Cancelled)
3. (Cancelled)
4. (Cancelled)
5. (Currently amended) The bisubstrate inhibitor of claim 1 wherein the peptide moiety has at least 4 contiguous amino acid residues selected from the sequence Lys Lys Lys Leu Pro Ala Thr Gly Asp Tyr Met Asn Met Ser Pro Val Gly Asp (SEQ ID NO:1), wherein the Tyr residue is modified so that a nitrogen atom replaces a hydroxyl to form the 2-amino-3-(4-amino-phenyl)-propionic acid residue.
6. (Currently amended) The bisubstrate inhibitor of claim 1 wherein the peptide moiety has at least 5 contiguous amino acid residues selected from the sequence Lys Lys

Lys Leu Pro Ala Thr Gly Asp Tyr Met Asn Met Ser Pro Val Gly Asp (SEQ ID NO:1), wherein the Tyr residue is modified so that a nitrogen atom replaces a hydroxyl to form the 2-amino-3-(4-amino-phenyl)-propionic acid residue.

7. (Currently amended) The bisubstrate inhibitor of claim 1 wherein the peptide moiety comprises the sequence Lys Lys Lys Leu Pro Ala Thr Gly Asp Tyr Met Asn Met Ser Pro Val Gly Asp (SEQ ID NO:1), wherein the Tyr residue is modified so that a nitrogen atom replaces a hydroxyl to form the 2-amino-3-(4-amino-phenyl)-propionic acid residue.

8. (Cancelled)

9. (Cancelled)

10. (Original) The bisubstrate inhibitor of claim 1 wherein the peptide moiety comprises a membrane translocating sequence (MTS).

11. (Original) The bisubstrate inhibitor of claim 10 wherein the MTS is at the N-terminus of the peptide moiety.

12. (Original) The bisubstrate inhibitor of claim 10 wherein the MTS is at the C-terminus of the peptide moiety.

13. (Original) The bisubstrate inhibitor of claim 1 wherein the peptide moiety comprises an HIV TAT sequence.

14. (Cancelled)

15. (Currently amended) A bisubstrate inhibitor of insulin receptor kinase, ~~comprising:~~

~~a nucleotide or nucleotide analog moiety;~~

~~and a peptide moiety which is a substrate for said insulin receptor kinase;~~

~~wherein said moieties are linked by a tether that comprises a proton donor;~~

~~wherein the tether is greater than or equal to 4.9 Å measured from a gamma phosphorus of the nucleotide or nucleotide analog moiety to the proton donor;~~

wherein the bisubstrate inhibitor of insulin receptor kinase is Compound 2.

16-57. (Cancelled)

58. (Original) The bisubstrate inhibitor of claim 1 which is bound to insulin receptor kinase.

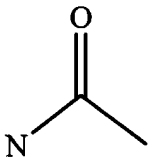
59. (Cancelled)

60. (Currently amended) A bisubstrate inhibitor of a protein kinase comprising:

a ~~nucleotide or~~ nucleotide analog moiety ~~comprising a triphosphate~~ consisting of γ-S-ATP; and

a peptide moiety which is a substrate for said protein kinase and which comprises ~~a tyrosine residue,~~ a 2-amino-3-(4-amino-phenyl)-propionic acid residue or ~~, a serine residue,~~ a 2,3-diamino-propionic acid residue, ~~a threonine residue, or a 2,3-diamino-butyric acid residue~~;

wherein said moieties are linked by a tether, wherein said tether is linked to the ~~tyrosine residue via its phenolic oxygen, to the~~ 2-amino-3-(4-amino-phenyl)-propionic acid residue via its aniline nitrogen, ~~to the serine residue via its hydroxyl oxygen,~~ or to the 2,3,diamino-propionic acid residue via its 3-amino nitrogen, ~~to the threonine residue via its hydroxyl oxygen, or to the 2,3-diamino-butyric acid via its 3-amino nitrogen,~~ and wherein said tether is linked to the ~~nucleotide or~~ nucleotide analog moiety via the gamma phosphate of said γ-S-ATP ~~the triphosphate~~, wherein the tether is



~~greater than or equal to 4.9 Å measured from a gamma phosphorus of the nucleotide or nucleotide analog to a proton donor of the tether formed by the phenolic oxygen, the aniline nitrogen, the hydroxyl oxygen, or the 3-amino nitrogen~~.

61. (Cancelled)

62. (Cancelled)

63. (Currently amended) The bisubstrate inhibitor of claim 60 wherein the protein kinase is a tyrosine protein kinase and the peptide comprises a tyrosine residue, wherein the tyrosine residue is modified so that a nitrogen atom replaces a hydroxyl to form the 2-amino-3-(4-amino-phenyl)-propionic acid residue.

64. (Cancelled)

65. (Cancelled)

66. (Cancelled) ~~The bisubstrate inhibitor of claim 63 wherein a nitrogen atom replaces a hydroxyl oxygen on the tyrosine~~.

67. (Original) The bisubstrate inhibitor of claim 60 which is bound to the protein kinase.

68. (Cancelled)

69. (Currently amended) The bisubstrate inhibitor of claim 60 wherein the peptide moiety comprises at least 4 contiguous amino acids of a natural substrate of said protein kinase wherein the peptide moiety comprises either a tyrosine residue that is modified so that a nitrogen atom replaces a hydroxyl to form the 2-amino-3-(4-amino-phenyl)-propionic acid residue or a serine residue that is modified so that a nitrogen atom replaces a hydroxyl to form a 2,3-diamino-propionic acid residue.

70. (Currently amended) The bisubstrate inhibitor of claim 60 wherein the peptide moiety comprises at least 5 contiguous amino acids of a natural substrate of said protein kinase, wherein the peptide moiety comprises either a tyrosine residue that is modified so that a nitrogen atom replaces a hydroxyl to form the 2-amino-3-(4-amino-phenyl)-propionic acid residue or a serine residue that is modified so that a nitrogen atom replaces a hydroxyl to form a 2,3-diamino-propionic acid residue.

71. (Currently amended) The bisubstrate inhibitor of claim 60 wherein the peptide moiety comprises at least 6 contiguous amino acids of a natural substrate of said protein kinase, wherein the peptide moiety comprises either a tyrosine residue that is modified so that a nitrogen atom replaces a hydroxyl to form the 2-amino-3-(4-amino-phenyl)-propionic acid residue or a serine residue that is modified so that a nitrogen atom replaces a hydroxyl to form a 2,3-diamino-propionic acid residue.

72. (Cancelled)

73. (Cancelled)

74. (Currently amended) The bisubstrate inhibitor of claim 60 wherein the peptide moiety is a natural substrate of said protein kinase, wherein the peptide moiety comprises either a tyrosine residue that is modified so that a nitrogen atom replaces a hydroxyl to form the 2-amino-3-(4-amino-phenyl)-propionic acid residue or a serine residue that is modified so that a nitrogen atom replaces a hydroxyl to form a 2,3-diamino-propionic acid residue.

75. (Cancelled)

76. (Cancelled)

77. (New) A method of making a candidate bisubstrate inhibitor of insulin receptor kinase, comprising:

synthesizing a peptide comprising a nitrophenylalanine residue;

reducing the nitro group on said nitrophenylalanine residue to form an amine group;

bromoaceteylating the amine group to form a bromide group;

displacing the bromide group by a phosphorothioate of ATPγS

78. (New) A method of making a candidate bisubstrate inhibitor of a protein kinase comprising:

synthesizing a peptide comprising a residue selected from the group consisting of a nitrophenylalanine residue and a diamino propionic acid residue;

reducing the nitro group on said nitrophenylalanine residue to form an amine group, if the peptide comprises a nitrophenylalanine residue;

bromoacetylating the amine group on said residue to form a bromide group;

displacing the bromide group by a phosphorothioate of ATPγS

79. (New) The method of claim 77 wherein the peptide is selected from the group consisting of:

KKKLPATGD-nitrophenylalanine-MNMSPVGD,

TGD-nitrophenylanaine,

GD-nitrophenylanaine-M,

D-nitrophenylanaine-MN,

nitrophenylanaine-MNM,

ATGD-nitrophenylanaine,

TGD-nitrophenylanaine-M,

GD-nitrophenylanaine-MN,

D-nitrophenylanaine-MNM,

nitrophenylanaine-MNMS,

PATGD-nitrophenylanaine,

ATGD-nitrophenylanaine-M,

TGD-nitrophenylanaine-MN,

GD-nitrophenylanaine-MNM,
D-nitrophenylanaine-MNMS,
nitrophenylanaine-MNMSP,
LPATGD-nitrophenylanaine,
PATGD-nitrophenylanaine-M,
ATGD-nitrophenylanaine-MN,
TGD-nitrophenylanaine-MNM,
GD-nitrophenylanaine-MNMS,
D-nitrophenylanaine-MNMSP, and
nitrophenylanaine-MNMSPV.

80. (New) The method of claim 77 further comprising the step of testing the candidate bisubstrate inhibitor in kinase assays to determine potency of inhibition.

81. (New) The method of claim 77 further comprising the step of testing the candidate bisubstrate inhibitor in kinase assays to determine specificity of inhibition.

82. (New) The method of claim 78 wherein the peptide is selected from the group consisting of: known phosphorylation sites of kinase enzymes, wherein a nitrophenylalanine is substituted for a tyrosine residue or a diaminopropionic acid residue is substituted for a serine residue.

83. (New) The method of claim 78 wherein the peptide is selected from the group consisting of:

KKKLPATGD-nitrophenylalanine-MNMSPVGD,
TGD-nitrophenylanaine,
GD-nitrophenylanaine-M,
D-nitrophenylanaine-MN,
nitrophenylanaine-MNM,
ATGD-nitrophenylanaine,
TGD-nitrophenylanaine-M,
GD-nitrophenylanaine-MN,

D-nitrophenylanaine-MNM,
nitrophenylanaine-MNMS,
PATGD-nitrophenylanaine,
ATGD-nitrophenylanaine-M,
TGD-nitrophenylanaine-MN,
GD-nitrophenylanaine-MNM,
D-nitrophenylanaine-MNMS,
nitrophenylanaine-MNMSP,
LPATGD-nitrophenylanaine,
PATGD-nitrophenylanaine-M,
ATGD-nitrophenylanaine-MN,
TGD-nitrophenylanaine-MNM,
GD-nitrophenylanaine-MNMS,
D-nitrophenylanaine-MNMSP,
nitrophenylanaine-MNMSPV,
LRRA-diaminopropionic acid-LG,
RRA-diaminopropionic acid,
RA-diaminopropionic acid-L,
A-diaminopropionic acid-LG,
LRRA-diaminopropionic acid,
RRA-diaminopropionic acid-L,
LRRA-diaminopropionic acid-L,and
RRA-diaminopropionic acid-LG.

84. (New) The method of claim 78 further comprising the step of testing the candidate bisubstrate inhibitor in kinase assays to determine potency of inhibition.
85. (New) The method of claim 78 further comprising the step of testing the candidate bisubstrate inhibitor in kinase assays to determine specificity of inhibition.

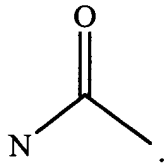
86. (New) The method of claim 77 wherein the peptide is selected from the group consisting of: known phosphorylation sites of insulin kinase enzymes, wherein a nitrophenylalanine is substituted for a tyrosine residue.

87. (New) An inhibitor of insulin receptor kinase, comprising:

a nucleotide analog moiety consisting of γ-S-ATP; and

a peptide moiety which comprises a 2-amino-3-(4-amino-phenyl)-propionic acid residue;

wherein said moieties are linked by a tether, wherein said tether is linked to the 2-amino-3-(4-amino-phenyl)-propionic acid residue via its aniline nitrogen and wherein said tether is linked to the nucleotide analog moiety via the gamma phosphate of said γ-S-ATP , wherein the tether is



88. (New) An inhibitor of a protein kinase comprising:

a nucleotide analog moiety consisting of γ-S-ATP; and

a peptide moiety which comprises a 2-amino-3-(4-amino-phenyl)-propionic acid residue or a 2,3-diamino-propionic acid residue;

wherein said moieties are linked by a tether, wherein said tether is linked to the 2-amino-3-(4-amino-phenyl)-propionic acid residue via its aniline nitrogen, or to the 2,3,diamino-propionic acid residue via its 3-amino nitrogen, and wherein said tether is linked to the nucleotide analog moiety via the gamma phosphate of said γ-S-ATP, wherein the tether is